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# MENTAL HEALTH AND THE ELDERLY: NEW BIOPHARMACEUTIC CONSIDERATIONS

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by Bernard E. Cabana

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**Prologue:** In a world where high technology reigns supreme, the pharmaceutical industry has been on the cutting edge of change, developing new products that serve the twin goals of improving medical care and generating profit. Without question, as this industry has evolved, its products and procedures have become more complex as a consequence of a growing knowledge base and a federal regulatory agency that takes very seriously its statutory charge to insure the safety and efficacy of drugs. Until February, 1983, Bernard E. Cabana worked for the Food and Drug Administration (FDA) as director of its Division of Biopharmaceutics in the National Center for Drugs and Biologics. Cabana, who holds a Ph.D. in pharmacology and was named to the Senior Executive Service during his tenure at FDA, is above all a scientist. While serving at the FDA, he pursued with a religious fervor the importance of bioequivalence in pharmaceutical products that are depicted as similar. That fervor, of course, placed him at the center of the continuing controversy pitting generic drugs against brand-name drugs. Cabana is strongly of the view that the generic versus brand name controversy is no longer simply an issue of cost or company. Advances in biopharmaceutics - a relatively new scientific discipline which studies the relationship of a drug's form and chemical properties to the effects it produces in patients - demands closer attention to which kind of drug is prescribed for what sort of patient. In other words, there is a need to fine tune drug therapy that did not exist a decade ago. Cabana currently runs his own company. His article was adapted from a paper originally delivered at a Project HOPE conference on Practical Approaches for Meeting the Mental Health Needs of the Elderly.

## 34 HEALTH AFFAIRS

In the past ten years, new technologies have advanced our knowledge of drug products and how they affect the body. We can now select medications, calibrate dosages, and monitor their therapeutic or toxic impact far more effectively than before. Many adverse or harmful reactions can be avoided.

Improvements in the technology of biological analysis have demonstrated the variations characteristic of distinct patient populations. The elderly and children, for example, differ biologically from each other and from young adult patients. We can no longer assume that the amounts, forms, and labeling of drugs as approved by the Food and Drug Administration (FDA) apply equally to all patients.

The mentally ill and elderly are among patients at greatest risk. Psychotropic drugs are frequently prescribed for older persons but their effects may not be adequately understood. The 1979 Task Force Report of the American College of Neuropsychopharmacology points out that "often any aberration in clinical symptoms, i.e., loss of effectiveness or toxicity . . . is ascribed to the idiosyncrasies of the patient and rarely ascribed to differences in drug products."<sup>1</sup>

Advances in bioanalytical technology now permit us to analyze minute quantities of a substance and to better understand its interaction with the body. Other important developments include high pressure liquid chromatography, radioimmunoassay, stable-isotope mass spectrometry, and genetic engineering. Together, these advances have important implications for the practice of clinical medicine. For example, drugs can now be administered in forms that release gradually over several days or that assure a constant level of protection. Our ability to measure small changes in the amount or effect of a drug means that we can prescribe for and monitor patients much more precisely. This new knowledge creates new responsibilities and new concerns.

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### Biopharmaceutics

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Biopharmaceutics is a relatively new scientific discipline which studies the relationship of a drug's form and physico-chemical properties to the effects it produces in patients. Understanding this relationship enables us to test whether a drug actually performs as intended. Biopharmaceutics includes the study of biological availability or bioavailability. In general terms, this is the rate and extent to which an active drug is absorbed into the patient's bloodstream. Another important area is the study of pharmacokinetics, the ways in which the body processes a drug. Generally these are known as the ADME processes: absorption, distribution, metabolism, and excretion.

The extent and rate of absorption, for example, are of the greatest importance in prescribing medication. Substituting a different form of a

drug that had a different rate of absorption can produce a toxic reaction or may conversely provide too low a level to have any therapeutic effect.

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### **Brand Name And Generic Drugs**

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Ten years ago, the major controversy in selecting drug products was the choice between lower cost generic drugs or higher priced brand name drugs. Today, the advances in biopharmaceutics have added new dimensions to the problem. It is no longer simply an issue of cost or company.

The FDA established a research program to apply the new knowledge and techniques to make therapeutic equivalence determinations about drugs via bioequivalence testing. Some manufacturers, both large, research-intensive firms and relatively small generic manufacturers, fully endorse the need for drug bioavailability and pharmacokinetics studies. Other firms regard this issue at best as a necessary evil imposed by the FDA.

In developing its biopharmaceutics program, the FDA was faced with two major tasks. The first was to identify those drugs and dosage forms which presented a potential problem; the second was the need to look again at drugs previously approved by the agency. Recent cutbacks in government-sponsored research dollars, together with the need to develop sophisticated technology to solve the many still-unanswered problems, have now made it impossible for the FDA to render a therapeutic equivalence determination for many drugs currently on the market. This problem requires attention from the pharmaceutical industry, academia, and research institutes.

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### **Equivalents And Alternatives**

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Two drugs are pharmaceutically equivalent if they have the same active ingredient and the same dosage form. Drugs with the same active ingredient but different dosage forms (for instance a tablet and a capsule) are pharmaceutical alternatives. The purpose of a bioequivalence study is to decide whether drug products that are pharmaceutically equivalent can in fact be used interchangeably to achieve the same therapeutic effects.

In 1975 the Food and Drug Administration proposed regulations to establish bioavailability/bioequivalence requirements for all drugs which posed a known or potential problem. The regulations create a petition mechanism by which any interested party (including the FDA Commissioner) may propose a bioequivalence requirement for any drug if the drug meets certain scientific and medical criteria. The requirement would then be established through the formal administrative rulemaking procedures, subject to publication and comment. Among the established criteria are documented therapeutic failure, documented bioequivalence, narrow therapeutic ratio, medical determination of serious adverse ef-

## 36 HEALTH AFFAIRS

fects in treatment or prevention of a serious disease, and such problems as low solubility or instability in the gastrointestinal tract.

Employing these criteria, the FDA has identified dosage forms which present potential as well as known problems. These include enteric-coated dosages, controlled release dosages, suppositories, and certain intramuscular drugs. Since such dosages present inherent equivalence problems, the FDA does not give them a therapeutic equivalence determination. The agency urges against the indiscriminate substitution of such dosages without careful patient monitoring and counseling.

The FDA has also added drugs to this "problem list" if they are related to a drug known to cause problems and have similar structural and physicochemical characteristics. This decision is not without controversy. Some groups, such as the American Association of Retired Persons, have felt that the FDA is far too conservative in approaching the problem. But others, such as the Pharmaceutical Manufacturers Association, have recommended that therapeutic equivalence be judged only for those specific drugs which have been tested.

During the past five years, the agency has documented problems with an additional forty-five drugs that were listed as potential problem drugs. Very few drugs not originally listed in the 1975 rule have subsequently been shown to have problems. Where bioequivalence has not been demonstrated for all manufacturers of any specific drug, the agency cannot assure the therapeutic equivalence of all versions of the drug.

When dealing with drugs of known or potential bioavailability problems, physicians and pharmacists should continue to prescribe and dispense generic drugs, but should be careful about switching a patient from one brand to another.

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### Safety And Efficacy

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In many diseases, the difference between an effective drug dose and a toxic dose is narrow. Often the consequences of an apparently "insignificant" alteration in drug particle size or drug dissolution are not fully appreciated even by pharmaceutical scientists. For example, the United States Pharmacopoeia recently changed certain specifications for dicumarol, a potent anticoagulant. The particle size requirement for the bulk drug and a dissolution specification for the finished dosage forms (tablets and capsules) were altered. Both the manufacturer of the capsule and of the tablet, two different large brand-drug companies, attempted to comply with the new specification.

One manufacturer discovered that the relative bioavailability of the tablet dosage form now differed from the presently marketed form by more than 30 percent. The capsule and the tablet were deemed by the agency to be no longer interchangeable. For a patient at risk of internal

hemorrhage or, on the other hand, a clot that could cause an embolism, the consequences of switching from a capsule to a tablet could be death.

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### Bioavailability And Individual Patients

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In recent years, the FDA has recognized bioequivalence as a vital concern in drug development. But in determining equivalence, a close correspondence of mean concentrations in the blood is not sufficient to indicate interchangeability. Because individuals differ so markedly, the FDA has promulgated a "75/75 Percent Rule" for several drug classes.<sup>2</sup> This requires that each individual subject be utilized as his own control in comparing the drug being tested with a reference drug thought to be its equivalent. For instance, two forms of lithium carbonate, a potent psychotropic drug used in the treatment of manic depression, were compared in a number of individual healthy volunteers. The mean bioavailability of the two lithium carbonate products was almost the same and would appear at first glance to demonstrate that the two products could be used interchangeably. But the bioavailability of one product as compared to the other in an individual subject actually ranged from 46-239 percent. Eight of eighteen subjects fell outside the acceptable range of 75-125 percent bioavailability. The lesson is that the similarity of the mean bioavailability of two products does not mean that they are bioequivalent. Such differences in critically ill patients could result in either serious harm or ineffectiveness.

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### The Mentally Ill And Elderly

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These concerns are especially important in the clinical use of psychotropic drugs. The nature of the patient population, the need for chronic use of such drugs, and the extensive metabolism of many psychotropic drugs suggest that great care be taken in choosing and monitoring drugs for the mentally ill and the elderly.

The consequences of inappropriate drug levels are severe. Subtherapeutic levels of chlorpromazine (an antipsychotic medication) can mean a continuation of the psychotic state. Too high a level can lead to extraparametrical side effects, an often debilitating and highly unpleasant condition with no additional therapeutic benefits. Either too high or too low a level of phenytoin, an anticonvulsant, can result in seizures. Insufficient levels of tricyclic antidepressants will fail to arrest depression, but too much can cause arrhythmias.

For the elderly patient, these concerns are magnified. Due to altered physiology, the geriatric patient is a great risk. Aging is generally associated with altered gastrointestinal physiology, decreased renal function, and slowed liver metabolism. Unless drug choice and dosage are appro-

## 38 HEALTH AFFAIRS

priate, drug accumulation in the body can cause serious adverse reactions.

As a general rule, the dosage for many drugs should be reduced two- to three-fold in the elderly patient who has normal kidney and liver functions. Where a patient has a disease or altered physiological functions, further reduction is needed to avoid serious toxicity.

To cite one instance, recent studies with Oraflex (benoxaprofen), a new anti-inflammatory drug used in the treatment of arthritis, have shown<sup>3</sup> a five- to seven-fold decrease in drug elimination in uremic patients.<sup>3</sup> The altered renal physiology of elderly patients can result in serious cholestatic jaundice or even death.

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### Clinical Plasma Monitoring

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Given the nature of mental illness and the potential alterations in physiology for the elderly, close monitoring of the blood levels of psychotropic medications and other critical drugs is strongly recommended. There is an absolute need to define the therapeutic zone of drugs in such patients and to monitor plasma level to adjust dosage. As we now use clinical chemistry in the routine practice of internal medicine, in the future we must learn to utilize plasma monitoring for diagnosis and dosage in geriatric and mental patients

#### NOTES

1. T. Itil, B.E. Cabana, and A. DiSanto, "Final Task Force Report on Bioavailability and Bioequivalence of Psychotropic Drugs," (Nashville, Tenn.: American College of Neuropsychopharmacology, 1979).
2. B.E. Cabana, "Assessment of 75/75 Rule: FDA Viewpoint," *Journal of Pharmaceutical Sciences* 72 (1983): 98.
3. B.M. Goudie et. al., "Jaundice Associated with the Use of Benoxaprofen," *The Lancet*, 24 April 1982: 959.